

Evidence Report

PHYSICAL AND CHEMICAL ASPECTS OF SALIVA AS INDICATORS OF RISK FOR DENTAL CARIES IN HUMANS

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I. INTRODUCTION

Overview

Dental caries remains a widely prevalent bacterial infection despite tremendous advances in its prevention and treatment. Although not a life-threatening condition, dental caries nonetheless has considerable impact on quality of life issues for both the individual and society as a whole. Pain, diminished function and esthetics, as well as time lost from routine daily activities are among the chief sequelae of caries. In terms of health care costs alone, treatment of dental caries and the attendant tooth morbidity and mortality comprises a significant portion of total US expenditures on health care. The important question why caries still continues to be a major public health problem remains unanswered. An approach to gain possible insights into this unanswered question is the assessment of the risk factors that are associated with caries. This report evaluates salivary parameters as probable risk factors.

Goal of the Report

The main purpose of this report is to help clinicians make informed decisions about saliva risk assessment in caries management. Saliva is assumed to be protective against caries and this report provides a systematic review of the clinical evidence that either does or does not support this assumption. The authors formulated four specific questions to evaluate various possible relationships between saliva and caries. In doing so the authors were guided by one key principle; that is, to summarize literature that would have relevance to clinicians. Information from purely in vitro or animal studies were not reviewed.

Background and Scope of the Problem

The general term "saliva" refers to the oral fluid that surrounds all oral hard and soft tissues. This oral fluid represents a mixture of fluids and components since it is derived from several sources. Major and minor salivary glands make the bulk contribution to oral fluid. Usually minor contributions originate from non-glandular sources such as crevicular fluid, oral microorganisms, host-derived cells and cellular constituents as well as diet-related components. The technical term most widely used to describe this oral fluid is "whole saliva" to differentiate this fluid from pure glandular salivas or glandular secretions. The largest contributors in terms of fluid volume, quantity of electrolytes and organic constituents are the six major salivary glands comprised of two parotid, two submandibular and two sublingual glands. Other sources of exocrine salivary constituents are the multiple minor salivary glands distributed underneath various soft tissues of the oral cavity. Functional effects of whole saliva are most likely due to exocrine but could also be related to non-exocrine derived constituents of oral fluid.

In order to understand the biochemistry of specific salivary constituents of exocrine origin research has focused on the analyses of glandular secretions. This effort resulted in a fairly comprehensive characterization of electrolyte composition, small organic molecules as well as macromolecules present in major salivary secretions. Basic salivary research relevant to the development of caries has mainly focused on the mineral homeostasis of the tooth surface and on anti-microbial systems effective against cariogenic bacteria.

It is well recognized that the integrity of calcium phosphate minerals such as hydroxyapatite, the predominant mineral phase of the tooth surface, is dependent on the pH and the buffering capacity of the surrounding fluid. While all salivary secretions are hypotonic they all contain bicarbonate, phosphate and many organic constituents which all contribute to salivary pH and buffering capacity. In addition, saliva contains calcium and phosphate in concentrations rendering this body fluid supersaturated with respect to all calcium phosphate salts. The consequence of this supersaturation establishes thermodynamic driving forces which are favorable to remineralization and unfavorable to demineralization. This feature is considered to be of fundamental importance in the remineralization capacity of saliva and is therefore believed to be critical for the repair of incipient caries lesions. This kind of supersaturation of saliva is clearly beneficial for processes requiring mineralization but could also lead to unwanted precipitation and epitactic growth of exposed mineral surfaces. The fact that the former process occurs but the latter does not occur in the oral cavity raised important questions. What is the biological basis to achieve this level of supersaturation and what is the biological mechanism by which spontaneous precipitation or epitactic crystal growth are prevented in the oral cavity? With the discovery and characterization of several major salivary phosphoproteins both of these questions could be answered. Functional studies showed in vitro that these proteins inhibit spontaneous precipitation and/or crystal growth in solutions supersaturated with respect to calcium and phosphate salts and also show selective adsorption to hydroxyapatite surfaces and thereby preventing unwanted mineral formation. The principal proteins belonging to this group are the acidic proline-rich proteins, statherin, histatin 1 present in both parotid and submandibular secretions and the phosphorylated cystatins found in submandibular secretions.

Another salivary domain deemed important to the caries process comprises several anti-microbial proteins present in salivary secretions. Classically, the anti-microbial salivary defense components have been divided into the immune and the non-immune host defense systems. Among the immunoglobulin classes, sIgA, IgA, IgG, and IgM have been identified in saliva. Secretory IgA (sIgA) is clearly a secretory product and the major immunoglobulin found in saliva. Much effort has been made to quantify individual immunoglobulins, to measure immunoglobulin fractions exhibiting specificity to cariogenic bacteria such as the *S. mutans* group and to develop a caries vaccine. In animal studies it could be shown that active immunization is a potent method interfering with the development of caries. Passive administration of antibodies in a variety of ways has also demonstrated to be protective in animals. Preliminary trials in human subjects have indicated that active mucosal immunization can give rise to specific mucosal antibodies to *S. mutans* antigens. Such antibodies may interfere with the accumulation of mutans Streptococci on teeth potentially resulting in reductions in dental caries.

The non-immune or innate host defense system of saliva comprises several salivary proteins exhibiting anti-bacterial and anti-fungal properties in vitro. The major proteins known to belong to this group are lysozyme, lactoferrin, salivary peroxidase, histatins and to some extent mucins. To what extent these anti-microbial proteins are active in the oral environment is still an open question and the subject of ongoing research. Nevertheless, the constant and immediate availability of innate host defense proteins and peptides has made them attractive candidates to be exploited therapeutically.

There are several confounding aspects associated with studies attempting to correlate salivary parameters and disease development. Caries is a multifactorial disease of which salivary parameters represent only a fraction of all contributing factors. Furthermore, salivary compositions show considerable inter-subject variations and unlike the compositions of other body fluids are dependent on flow rate which in turn is regulated almost exclusively by the autonomic nervous system. In

addition, the likelihood that a specific salivary parameter can be identified as the causative agent for caries development in vivo is very small. This consideration is based on the fact that the salivary system exhibits several levels of redundancies (Figure 1). At the morphological level there is redundancy by the presence of more than one major salivary gland and that the major glands occur in pairs. Some salivary constituents are specific for one type of gland but others occur in more than one type of glandular secretion. On the molecular level there is functional redundancy since different salivary proteins can display similar functional characteristics. There is also molecular redundancy with respect to individual salivary proteins, which has an evolutionary basis. Most salivary proteins have evolved into families of polymorphic forms. Within each of such a protein family the individual members differ structurally in minor ways but exhibit almost the same functional characteristics. It has become clear that these multiple levels of redundancies in the salivary system introduce great difficulties for the identification of specific salivary parameters as disease risk factors. There is little doubt, however, that each of the salivary constituents makes a contribution to the overall salivary functional capacity.

II. METHODOLOGY

Objectives and Questions

The etiology and pathogenesis of dental caries are known to be multifactorial. Despite the fact that the salient etiological components important for the development of caries have been identified, the interplay between intrinsic and extrinsic factors is still not fully understood. As in other host-parasite interactions, there appear to be marked variations in individual susceptibility towards disease. This variability in susceptibility is responsible for significant reductions of caries incidence in some individuals while others exhibit high incidence of the disease. Intrinsic host factors likely play a key role in modulating the initiation and progression of caries. The objective of this evidence report is to provide a critical evaluation of the role and effects of saliva in the pathogenesis of caries.

The general question addressed is: "Is there clinical evidence for a protective effect of saliva against caries?" The evaluation of saliva as a risk factor for caries is complicated, however, by the fact that saliva is a complex body fluid which shows considerable intra- and inter-subject variability with respect to chemical and physical properties. In addition, a number of medical conditions lead to salivary alterations which, in turn, may increase the risk for caries in those affected individuals. Therefore, to develop an adequate and comprehensive search strategy the following four questions were addressed. For each of these questions primary, mixed and/or permanent dentitions in subjects of all ages were examined.

(1) Are individuals with teeth and altered salivary physiology at increased risk for dental carious lesions compared with individuals of the same age and dentition with normal salivary physiology?

(2) Are individuals with teeth and altered salivary electrolyte biochemistry at increased risk for dental carious lesions compared with individuals of the same age and dentition with normal salivary electrolyte biochemistry?

(3) Are individuals with teeth and altered salivary composition with respect to macromolecules at increased risk for dental carious lesions compared with individuals of the same age and dentition with normal salivary macromolecular composition?

(4) Are individuals with teeth and diagnosed medical conditions/diseases which affect saliva at increased risk for dental carious lesions compared with individuals of the same age and dentition who do not have medical conditions/diseases which affect saliva?

Search Strategy and Databases

Sources

We used broad-based literature searching in the two electronic databases MEDLINE and EMBASE to ensure that we found all potentially relevant information. Search terms included those key words relevant for saliva in the diagnosis and etiology of caries. Results were checked for retrieval of several key articles which were decided upon a priori. Search dates depended on the database, but ranged from 1970 to August, 2000. One broad caries hedge was used with each of four saliva hedges developed, respectively, for the four focused questions. This resulted in the retrieval of eight separate sets of literature comprising a total of 3,086 articles. In addition, we conducted hand searches of article bibliographies and abstracts from scientific meetings that were not retrieved initially (IADR/AADR, ICOB, and ORCA). To a limited extent we also sought opinion and guidance from experts in the field.

Initial Results from Database Searches

The search for literature under Question Number 1 (salivary physiology) yielded 1,573 citations, including duplicates. This consisted of 1,330 citations from MEDLINE and 243 citations from EMBASE. The search for literature under Question Number 2 (salivary electrolytes and small molecules) yielded 373 citations from MEDLINE and 42 citations from EMBASE (n=415). The search for literature under Question Number 3 (salivary macromolecules) yielded 357 citations from MEDLINE and 122 citations from EMBASE (n=479). The search for literature under Question Number 4 (specific medical conditions affecting salivary function) yielded 408 citations from MEDLINE and 211 citations from EMBASE (n=619). Approximately 150 additional articles or abstracts were evaluated as part of the hand searching process.

Selection Process and Inclusion/Exclusion Criteria

This systematic review was complicated by the initial retrieval of an enormous volume of potentially relevant information. Most of the information we found would provide equivocal evidence, mainly due to variations in experimental design and data analysis or due to the low number of subjects evaluated. An iterative approach was therefore utilized to refine the search.

As a first approximation, we used broad criteria to maximize the retrieval process. Our initial search results included titles and abstracts of all article types written in English and involving humans, from 1970 to August, 2000. One person then screened titles and abstracts for inclusion criteria and to identify duplicates. If there was any doubt about excluding a study at the title-abstract stage, it was not excluded. Following the exclusion of those articles clearly inappropriate to the review (e.g., caries or salivary status not clearly defined), an electronic bibliography software program was used to merge the original literature sets into one new set of about 600 titles and abstracts. The full-length articles were retrieved and subsequently subjected to a second round of screening with additional inclusion criteria, resulting in the final number of articles formally reviewed and included in the evidence tables. This resulted in further reduction of the number of articles germane to this review and comprised the following inclusion parameters: English language articles reporting original in vivo human studies with a defined control group, 1986 to August, 2000, with ≥ 30 total subjects. All longitudinal studies meeting these criteria were included. Otherwise, only articles satisfying Agency for Healthcare Research Quality (AHRQ) level II-3 or above were included. Consequently, purely descriptive studies of large subject populations have been excluded from the evidence tables; however, some of these are collectively described in the evidence report under "Other Relevant Evidence." Also described under this heading are several pertinent articles published prior to 1986 or that were not available for inclusion into the evidence tables prior to the deadline for submitting this report.

A complete listing of exclusion criteria is provided in Attachment A. It should be noted that many of the articles met more than one exclusion criteria. Specific exclusion criteria therefore were: articles not written in English, articles written before 1986, in vitro studies, animal studies, human in situ studies, AHRQ level III studies (including case reports); and articles with relatively low statistical power ($n < 30$ subjects). Additionally, articles or portions of articles which dealt with salivary microbiology, fluoride treatments, or food and nutrition factors were deemed beyond the scope of the present review and were also not comprehensively evaluated.

Abstraction and Check on Accuracy

Data Collection and Abstraction/Calibration Process

We developed a data extraction form (see Attachment B) to ensure the complete and consistent collection and abstraction of data. This form was used initially to facilitate our calibration and to allow fabrication of a preliminary evidence table. Once sufficient level of agreement between the abstractors was attained, data from the articles were entered directly into the evidence table without use of the data extraction form. Two persons independently abstracted data from each article to ensure accuracy of information retrieval and reporting. For each article a decision was made whether or not the study results were consistent with a protective effect due to saliva; for some articles a designation of "possibly" was indicated when the data were suggestive of, but not clearly discernible as a protective effect. Questions and disagreements about articles were resolved by discussion followed by a consensus decision between two abstractors.

Evidence Obtained by Category

Data were synthesized descriptively for each included article according to: (1) general description; (2) experimental design characteristics; (3) caries status assessments; (4) saliva status assessments; and (5) clinical evidence for the presence or absence of a protective effect of saliva against caries. The general description category included information about the data extraction source (article or abstract), the study funding, setting and length, and the AHRQ score. Under the category of experimental design characteristics were included data on the sampling method and response rate, the training and reliability of examiners, confounding factors and controls, blinding of examiners or subjects, the number of subjects lost and the reasons for the dropouts, and the statistical methods used to analyze the study data. Caries status assessments included tooth or dentition type (primary, mixed or permanent), the caries scoring and detection method, the caries location (crown or root), the caries extent (enamel or dentin), the caries process being described in the study (cavitated lesion or initial demineralization), and the indicators used by the investigators to define caries risk and to make any clinical decisions pertinent to the study. Saliva status assessments included the source of saliva (whole saliva or specific glandular secretions), the method used to stimulate salivary output (usually either chewing unflavored wax or rubber bands and/or use of lemon candy or topical 2% citric acid), and the chief salivary parameter described. Examples of the latter included salivary flow rate, buffer capacity, pH, and levels of inorganic and organic constituents. The final category which listed the actual clinical evidence included information on subject demographics (including any contributory medical conditions), a presentation of the main findings for each study, and summary information that included the authors' conclusions as well as explanatory comments by the reviewers. The reviewers also provided an overall appraisal of whether the study did or did not report evidence supporting any increased risk of caries.

Methodological Considerations in the Data Abstraction and Analysis

The included studies evaluated individuals from 25 different countries. When not specifically described in any given study, the racial/ethnic composition of the study groups was assumed based on the demographic information that was provided. This review may have some small degree of publication bias in that our review was limited to the available and obtainable studies that met

inclusion/exclusion criteria. Several of the included studies appear to be based on the same subject population and differ only in the types of experimental measures being reported; in these instances we have indicated this in the Comments column of the evidence table. In cases where separate publications were retrieved that described interim time-points of long-term longitudinal studies (ex. 4-, 8- and 12-year follow-ups), we included only the study reporting on the longest interval; however, where baseline and the final follow-up publications gave different results, we did include both the initial and final studies.

A moderate-to-high degree of heterogeneity in caries assessments was observed in the reviewed studies. Thus comparisons were made difficult by the lack of a uniform and standard definition of caries risk in those studies evaluating subjects who were “caries-active” (also termed caries-susceptible, caries-prone and high-caries subjects) vs. “caries-resistant” (also termed caries-inactive, caries-free and low-caries subjects). For example, some studies defined their high-caries group as having individuals with ≥ 5 carious lesions whereas others defined caries activity with as little as one carious lesion. Although most studies reported results in terms of standard decayed, missing or filled teeth and/or surfaces (DMFT; DMFS), this also was not uniformly applied throughout all studies. Moreover, some studies reported different types of associations with saliva when findings were evaluated separately according to the D, M, or F components. For many studies we inferred from the data that a cavitated lesion was the primary outcome variable in caries assessments. These issues notwithstanding, we have attempted to provide sufficient details within the evidence table to facilitate comparisons among the various studies.

Heterogeneity in saliva sampling techniques was not considered to be of major consequence since nearly all of the studies utilized a small number of fairly standard techniques and many of the studies controlled for diurnal variations in salivary output by standardizing the time of saliva collections. Except where specifically noted in the evidence table, we assumed that appropriate clinical, biochemical, and immunological analyses of saliva were performed.

Heterogeneity in the amount of experimental details provided in the various studies was significant. Unclear, unreported or missing data were indicated by a designation of “no data/not applicable” abbreviated as “ND/NA” in the evidence table. For example, an entry indicating the length of the study was not applicable for cross-sectional studies. For a few studies we found that the authors may have stated conclusions that were not consistent with the data presented; in these instances a note was made in the Comments section of the evidence table. We also noted distinctions between statistical significance and clinical relevance; for example, when salivary flow rates between two subject groups were statistically different but both were within normal physiologic limits.

We point out that none of the included studies describe tooth surface-adsorbed salivary components (i.e., acquired pellicle). This was a consequence of our search strategy which excluded studies that were entirely in vitro or were performed with animal models. The so called in situ studies wherein subjects wore intraoral test appliances also were excluded when the salivary status and caries status of the subjects were not provided in the report. For the same reason studies reporting data on pooled saliva samples were also excluded. Unfortunately, the result of these exclusions is that there exist quite a few excellent studies that contribute significantly to the field of salivary research, but which were beyond the stated goal of the present review. Finally, data from the various included studies were not analyzed quantitatively, and no Meta analysis was conducted as part of this evidence report.

III. RESULTS

Description and Quality Assessment of the Included Studies

A total of 96 references are included in the evidence tables, which independently detail the critical elements for each study (see Attachment C, Evidence Tables 1A-C). Two of the studies examined subjects from more than one country. The breakdown by country is: Australia (2); Belgium (2); Brazil (1); Canada (3); Croatia (1); Denmark (1); Ethiopia (1); Finland (17); France (2); Germany (3); Greece (2); Hungary (2); Iceland (2); India (5); Israel (3); Mexico (1); the Netherlands (2); Norway (1); South Africa (2); Spain (1); Sweden (23); Taiwan, Republic of China (1); Turkey (1); United Kingdom (5); and the United States (14).

We graded the reports using the AHRQ evidence scale. Among the included studies, 29 provided longitudinal measures of the study populations (range 9 months-12 years). Of these, 24 were graded as AHRQ level II-3 (i.e., descriptive studies with longitudinal measures but lacking a clearly defined comparison group), three could not definitely be differentiated between being AHRQ level II-3 or II-2 (i.e., longitudinal studies having clearly discernible test and control groups), and two could not definitely be differentiated between being AHRQ level II-3 or II-2 and AHRQ level III (i.e., cross-sectional descriptive studies without an adequate comparison group). Thus, of the 96 included studies, only three (3%) are true longitudinal cohort studies, 64 (67%) are true case-control cross-sectional studies, 24 (25%) are multiple cross-sectional descriptive samplings, and five (5%) are not clearly definable.

More than two-thirds of the studies made bivariate comparisons of various salivary parameters and caries status. Just under 30 studies (approx. 28%) utilized statistical tests that involve some type of multivariate analysis. Interestingly, a general trend was observed in that statistically significant relationships between salivary parameters and caries found in the bivariate analyses were often not demonstrated in the multivariate analyses. For individuals who are generally healthy medically, in particular, this suggests that the potential contribution of salivary parameters in establishing caries risk may be outweighed by other important factors such as a positive caries history, diet (high sugar intake), oral hygiene status (plaque score), frequency of dental visits, fluoride exposure, and the presence of high numbers of cariogenic microorganisms.

We note some concern over the statistical power in many of the studies. To be included in this review, studies must have had a minimum sample size of 30 subjects total. Nearly half of the studies (n=45) only had about 10-30 subjects divided into 1-4 groups, depending upon the experimental design. The range of total sample size ranged from 30-692 subjects. Dropout rates did not appear to be a significant problem in these studies. We note also that only 10 studies made any specific mention of examiner or subject blinding. Similarly, relatively few studies gave comprehensive information about sampling methods and response rates. Only two of the included studies analyzed self-reported oral dryness among the subjects so that any lack of correlation between subjective symptoms and clinical measurements of saliva was not an important issue in this review.

As part of our review we made an assessment whether or not the data reported in each study demonstrated an association between salivary factors and an increased risk of caries. We determined that 21 studies (22%) demonstrated sufficient evidence to establish some type of relationship between saliva and caries, that 25 studies (26%) reported weak or equivocal evidence which we deemed as "possibly" demonstrating a relationship between saliva and caries, and that 50 studies (52%) failed to show any such relationship. As also discussed below, weak or negative results complicate any review of the evidence. The usual concern is whether the lack of a demonstrated association results from its true absence or methodological factors which may have precluded its discovery. Our detailed summaries of the results for each of the four formulated questions are presented with this issue in mind.

Results for each of the Four Formulated Questions

The distribution of the principal studies describing physical and chemical aspects of saliva as indicators of risk for dental caries in humans is presented in Summary Table 1. Given the relatively

large number of articles reviewed, it is important to consolidate the myriad findings into a few tangible unifying concepts. Thus, the following discussion highlights the essential findings of the various studies, and the reader is referred to the evidence tables when additional information is desired. It should also be noted that a substantial number of the articles reviewed presented data which fell under more than one of our formulated questions. Consequently, these articles are described multiply in the results below. For example, most of the articles related to diseases that alter salivary physiology (Question 4) measured the salivary parameters of flow rate and buffer capacity (Question 1). In each instance, however, the predominant findings of the various studies are presented as appropriate for each of the four formulated questions.

Question Number 1: Are individuals with teeth and altered salivary physiology at increased risk for dental carious lesions compared with individuals of the same age and dentition with normal salivary physiology?

Salivary Flow Rate

Salivary flow rate is a clinical measure of the total secreted output of the salivary glands, either individually or in combination. There is reasonably good evidence that the risk for caries is significantly increased when salivary flow rate is pathologically low (ex. <0.8 - 1.0 ml/min stimulated whole saliva flow) for extended periods of time, that occurs in a number of medical conditions which lead to salivary gland dysfunction (see Question 4 below). Fifteen studies clearly showed a correlation between low salivary flow rate and dental caries experience [1-15]. An additional six studies reported a similar result although the data were not quite as strong [16-21]. All these 21 studies examined whole saliva and only three of them also examined parotid gland secretion (Najera et al., 1997; Pedersen et al., 1999; Ryberg et al., 1991), while none of them examined pure secretions from submandibular/sublingual or minor salivary glands. Most of these studies were cross-sectional comparisons between groups of individuals with either low vs. high caries activity and/or with normal vs. abnormal salivary flow. In studies where the salivary flow was quantified as a predictive measure for caries (for example, Holbrook et al., 1993, Vehkalahti et al., 1996), it appeared to have relatively poor sensitivity (≤ 0.20) and relatively good specificity (≥ 0.80). Collectively, the evidence indicates that clinically relevant chronic reduction in salivary flow rate is a strong risk factor for caries prevalence and incidence.

Although flow rate per se appears to be inversely related to caries experience, there is no clear consensus that the stimulation status of either whole saliva or pure glandular secretion is important in caries risk. The papers by Almstahl et al. (1999), Pedersen et al. (1999), and Ravald and List (1998), for example, found that individuals with significantly diminished flow rate (due to Sjögren's syndrome) of both unstimulated and stimulated whole saliva had increased numbers of filled carious lesions when compared to individuals with normal salivary flow. At least five other studies which only examined stimulated whole saliva flow rate found an inverse correlation with caries experience [2, 4-7]. In contrast, in the paper by Furhoff et al. (1998) the authors make a distinction between stimulation status and report that the flow rate of unstimulated whole saliva, but not that of stimulated whole saliva, is inversely related to caries experience. Similarly, Ohrn et al. (1999) reported a relationship between caries and unstimulated whole saliva flow rate, but not necessarily with stimulated flow rate. In the case of parotid secretions, both Najera et al. (1997) and Ryberg et al. (1991) found an inverse relationship between stimulated parotid secretion rate and caries experience. There is no clear evidence to suggest that the method of salivary stimulation (i.e., masticatory or gustatory) is related to caries risk.

Of the 21 studies reporting a relationship between salivary flow rate and caries, the majority examined coronal caries only. At least two studies specifically evaluated both crown and root caries [4, 11]. Ravald and List (1998) reported that both crown and root caries were related to diminished salivary flow rate. In contrast, Guivante-Nabet et al. (1999) reported an inverse caries relationship only between crown caries and flow rate. Thus, there is no clear consensus that the risk for caries

due to poor salivary flow rate is different for crown vs. root surfaces. Furthermore, there is no clear indication that occlusal vs. smooth crown surfaces have different caries susceptibilities as a result of low salivary flow.

Of the studies reporting a relationship between salivary flow rate and caries, roughly two-thirds examined only permanent teeth while the remainder examined primary and/or mixed dentitions. Only one paper (Johansson et al., 1992) clearly made a distinction between the caries susceptibility of primary vs. permanent teeth. These authors reported that there was an increased risk of caries in primary but not permanent teeth due to low salivary flow. Otherwise, there is no clear consensus that the risk for caries due to poor salivary flow rate is different for primary vs. permanent teeth.

More than 30 of the studies which evaluated salivary flow rate and caries failed to demonstrate an inverse relationship between the two [22-55]. However, this likely does not contradict the results just mentioned above because many of these studies had no differences in caries prevalence or incidence among the comparison groups, making moot any judgements about salivary flow rate as a risk for caries (for example, Meurman et al., 1997, Narhi et al., 1996, Narhi et al., 1999, Nasman et al., 1994, Pojhamo et al., 1988, Sepet et al., 1998, Swanljung et al., 1992, Touyz et al., 1993, Twetman et al., 1989, and Younger et al., 1998). Similarly, a number of these studies demonstrated intra- or intergroup differences in caries that may have been too small to discern any effect due to salivary flow (for example, Bergman and Ericson, 1986 and Sullivan, 1990). Conversely, in several of these studies the flow rates of the comparison groups were within normal limits (ex. >0.8-1.0 ml/min stimulated whole saliva flow), again making moot any judgements about salivary flow rate as a risk for caries (for example, Bergman and Ericson, 1986, Dodds et al., 1997, Faine et al., 1992, Lundgren et al., 1997, and Sgan-Cohen et al., 1992). In longitudinal studies investigating salivary flow as a predictor of caries increment, little or no predictive value was observed for individuals with normal salivary flow rates (for example, Bergman and Ericson, 1986, Fure, 1998, Lundgren et al., 1997) or when the study interval was relatively short, such as one year or less (for example, Demers et al., 1992, MacEntee et al., 1993, and Ratio et al., 1996). Curiously, at least one study reported that high, rather than low, salivary flow rate increased the risk of dental caries in noninsulin-dependent diabetics (Collin et al., 1998); however, this association did not appear to have clinical significance.

Taken together, the literature supports the belief that pathologically decreased salivary flow rate is a risk factor for dental caries, when both prevalence and incidence are evaluated. In patients with definite salivary gland dysfunction, low flow rate appears to be a good risk indicator and risk predictor for caries. However, the use of salivary flow rate to indicate or predicate caries risk in subjects with normal salivary physiology does not seem to be clinically useful. Probably, this reflects the increased importance of other factors such as dietary and oral hygiene habits as well as microbial load in determining caries susceptibility in subjects with normal salivary flow. The protective effect of salivary flow remains consistent, for the most part, regardless of the salivary source (whole saliva or glandular secretions) or stimulation status (stimulated or unstimulated; masticatory stimulation or gustatory stimulation). In short, lowered secretion rates (due to salivary gland hypofunction) tends to increase the caries risk.

Salivary Buffer Capacity and pH

Unlike the evidence available for salivary flow, there is only modest evidence that the risk for caries is significantly increased when the buffering components of saliva are not able to prevent or reverse acidic conditions in the mouth. This likely is due to the fact that diminished buffering capacity, in contrast with diminished salivary flow, is not clearly associated with any of the known salivary gland pathologies (see Question 4 below). Buffer capacity is distinguished from pH per se in the various studies in that the latter is a labile parameter highly influenced by the types and timing of food intake as well as oral hygiene habits whereas the former is a more useful measure of an individual's innate ability to maintain a neutral or slightly alkaline pH in saliva. The parameter of buffer capacity is

measured using a salivary pH endpoint in acid-base titrations. Individuals with lower, more acidic final pH value (ex. endpoint pH<5.0-5.5) are deemed to have diminished buffering capacity.

Seven studies clearly showed a correlation between low salivary buffer capacity and dental caries experience [4-7, 9, 15, and 38]. An additional four studies reported a similar result although the data were not quite as strong [19, 25, 56, 57]. All these 11 studies examined the buffer capacity of whole saliva and none of them examined pure secretions from parotid, submandibular/sublingual or minor salivary glands. These same 11 studies all examined the buffer capacity of stimulated whole saliva and only three of them also examined unstimulated whole saliva (Johansson et al., 1992; O'Sullivan and Curzon, 2000; and Ohrn et al., 1999). Most of these studies were cross-sectional comparisons between groups of individuals with either low vs. high caries activity and/or with normal vs. abnormal buffer capacity. In studies where the salivary buffer capacity was quantified as a predictive measure for caries (for example, Holbrook et al., 1993, Vehkalahti et al., 1996), it appeared to have relatively poor sensitivity (≤ 0.20) and relatively good specificity (≥ 0.80). Collectively, the evidence indicates that low salivary buffer capacity is, at best, a moderate risk factor for caries prevalence and incidence.

Although it appears that, for whole saliva, a low buffering capacity is correlated with caries experience, there is no clear consensus that the stimulation status per se of the whole saliva is important in caries risk. Of the three studies which examined the buffering capacity of both stimulated and unstimulated whole saliva, only the one by Ohrn et al. (1999) reported a relationship between caries and stimulated, but not unstimulated, whole saliva. In contrast, Johansson et al. (1992) and O'Sullivan and Curzon (2000) made no such distinction in their findings. The remaining studies which only examined stimulated whole saliva buffering capacity found an inverse correlation with caries experience [4-6, 15]. Given the lack of evidence concerning unstimulated whole saliva, it would be prudent to qualify the evidence as applying only to stimulated whole saliva. There is no clear evidence to suggest that the method of salivary stimulation (i.e., masticatory or gustatory) is related to caries risk.

Of the 11 studies reporting a relationship between salivary buffer capacity and caries, the majority only examined coronal caries while one study examined both crown and root caries (Guivante-Nabet et al., 1999) and another one examined only root caries (Faine et al., 1992). The findings reported by Guivante-Nabet et al. (1999) are the only data indicating an inverse relationship between buffer capacity and root caries, but not crown caries. Thus, there is no clear consensus that the risk for caries due to poor salivary buffer capacity is different for crown vs. root surfaces. Furthermore, there is no clear indication that occlusal vs. smooth crown surfaces have different caries susceptibilities as a result of low buffer capacity.

Of the studies reporting a relationship between salivary buffer capacity and caries, roughly two-thirds examined only permanent teeth while the remainder examined primary and/or mixed dentitions. Only one paper (Johansson et al., 1992) clearly made a distinction between the caries susceptibility of primary vs. permanent teeth. These authors reported that there was an increased risk of caries in primary but not permanent teeth due to low buffer capacity. Otherwise, there is no clear consensus that the risk for caries due to poor salivary buffer capacity is different for primary vs. permanent teeth.

When salivary pH was evaluated independent of buffer capacity, only three studies were found that clearly showed a correlation between salivary pH (ex. pH <6.5-7.0) and dental caries experience [5, 6, 58]. All three studies examined the pH of whole saliva and none of them examined pure secretions from parotid, submandibular/sublingual or minor salivary glands. Two examined the pH only of stimulated whole saliva (Holbrook, 1993 and Holbrook et al., 1993) and one examined the pH only of unstimulated whole saliva (Pajari 1988). These studies examined crown caries in both primary and permanent teeth. Collectively, the evidence indicates that low salivary pH is a poor-to-moderate risk factor for caries prevalence and incidence. Due to the little available evidence, no definitive statements can be made whether or not the stimulation status per se of whole saliva pH is important in caries risk. There is no evidence to suggest that the method of salivary stimulation (i.e.,

masticatory or gustatory) is related to caries risk. In addition, there is insufficient evidence to establish that the risk for caries due to low salivary pH is different for crown vs. root surfaces, different aspects of crown surfaces, or for primary vs. permanent teeth.

Approximately 30 of the studies which evaluated salivary buffer capacity and/or pH failed to demonstrate an inverse relationship between these two salivary parameters and caries experience [1, 17, 22, 24, 26, 28, 30, 32, 34-37, 39-42, 47-49, 51, 52, 54, 59-65]. Again, as discussed above for salivary flow rate, studies reporting a lack of correlation do not necessarily prove that a particular correlation does not in fact exist. Consequently, caution is needed interpreting the evidence based on such studies. Many of these studies had no differences in caries prevalence or incidence among the comparison groups, making irrelevant any judgements about salivary buffer capacity or pH as risks for caries (for example, Narhi et al., 1996, Narhi et al., 1999, Nasman et al., 1994, Pojhamo et al., 1988, Sepet et al., 1998, Swanljung et al., 1992, Touyz et al., 1993, Twetman et al., 1989, and Younger et al., 1998). Similarly, a number of these studies demonstrated intra- or intergroup differences in caries that may have been too small to discern any effect due to salivary buffer capacity or pH (for example, Bergman and Ericson, 1986; Stabholz et al., 1991; and Sullivan, 1990). Conversely, in several of these studies the buffer capacity and/or pH of the comparison groups were within normal limits, again precluding any definitive conclusions (for example, Bergman and Ericson, 1986, Dodds et al., 1997, Lundgren et al., 1997, and Sgan-Cohen et al., 1992).

To summarize this evidence in comparison with that of salivary flow rate, the literature is somewhat less definitive on the relationship between salivary buffer capacity or pH and caries. The parameter of buffer capacity appears to have some clinical usefulness but its value as a single measure of caries risk is not strong. It seems appropriate, therefore, to state that buffer capacity appears to be a weak-to-moderate indicator or predictor of caries risk when considered as a single independent variable. Static measures of salivary pH, separate from measures of buffer capacity, seem to have little practical value in ascertaining caries risk.

Salivary Sugar Clearance Rate

Only four studies specifically evaluated the relationship between oral glucose clearance time and caries [18, 32, 42, 66]. This parameter is typically measured by plotting the decrease in glucose concentrations over time following a standardized rinse. At least three additional studies provided single time-point measures of salivary glucose concentration [51, 52, and 54]. None of these articles showed any significant relationship between glucose concentration or clearance rate and caries. In the longitudinal study of Sundin et al. (1992), oral sugar clearance time was poorly correlated with three-year caries incidence. Based on this and the other studies, it appears that other factors such as dietary and oral hygiene habits as well as salivary microbiota outweigh glucose clearance rate in the determination of caries risk, especially when the latter is considered to be physiologically normal. Thus, the limited data available indicates no significant value of sugar clearance rate as a marker of caries risk.

Other Relevant Evidence

A descriptive study examining 71 community-dwelling 92-year-old subjects found that a slow oral sugar clearance rate was associated with a high proportion of untreated root caries lesions (Lundgren *et al.*, 1997). Another study which also examined oral sugar clearance found a slower rate in subjects with myotonic dystrophy, when compared to healthy controls, that was related to the high caries prevalence in the dystrophy patients (Engvall and Birkhed, 1997).

Question Number 2: Are individuals with teeth and altered salivary electrolyte biochemistry at increased risk for dental carious lesions compared with individuals of the same age and dentition with normal salivary electrolyte biochemistry?

Calcium, Phosphate, and Fluoride Concentrations

The caries process involves a progressive and, quite often, an ultimately irreversible alteration in the hydroxyapatite structure of the affected tooth. In this regard it seems logical to expect that the salivary concentrations of ions that comprise hydroxyapatite should be correlated with caries status in some way. It is surprising, therefore, that only seven studies were found that indicate an association between caries and the levels of either calcium, phosphate, or fluoride [12, 20, 21, 45, 46, 67, 68]. Duggal et al. (1991) reported an inverse relationship between fluoride concentration and caries status. [Again, we point out that studies examining fluoride treatment per se were not included in this review.] Four studies showed an inverse relationship between levels of salivary calcium and caries activity [12, 20, 21, 45], but this held true only for girls and not for boys in the two Woltgens et al. (1992) studies. The evidence concerning phosphate is less clear, partly because a clear distinction between organic vs. inorganic phosphorous is not always made. Pandey et al. (1990) reported increased levels of phosphorous and alkaline phosphatase activity in subjects with rampant caries compared to subjects with either non-rampant caries or no caries; however, interpretation of these data are confounded by the large standard deviations in electrolyte measurements. On the other hand, four other studies indicate an inverse relationship between salivary concentrations of organic or inorganic phosphorous and caries activity [20, 21, 45, and 46]. Again, however, this held true only for girls and not for boys in the two Woltgens et al. (1992) studies.

Two studies evaluated only unstimulated whole saliva [67, 68], two studies examined both unstimulated and stimulated whole saliva [20, 21], three studies evaluated only stimulated parotid saliva [24, 45, 46], and one study evaluated both stimulated whole saliva and stimulated parotid saliva [12]. None of these studies examined pure secretions from submandibular/sublingual or minor salivary glands. These studies examined crown caries in both primary and permanent teeth. Due to the little available evidence, no definitive statements can be made whether or not the salivary gland stimulation status is important in caries risk. There is no evidence to suggest that electrolytes secreted from a specific salivary gland or that the method of salivary stimulation (i.e., masticatory or gustatory) is related to caries risk. In addition, there is insufficient evidence to establish that the risk for caries due to low levels of critical electrolytes is different for crown vs. root surfaces, different aspects of crown surfaces, or for primary vs. permanent teeth.

In contrast to the above studies, two studies found no relationship between the concentration of salivary calcium and caries [24, 69]. It should be noted that the respective comparison groups also did not demonstrate significant differences in caries activity. Again, interpretation of these findings is not easy.

When taken together, there is very modest evidence to suggest that low levels of certain critical electrolytes may increase caries susceptibility, but the clinical applicability of this information as a way of establishing the risk of caries appears premature at this time. In particular, more information is needed on the range of normal values of these electrolytes so that judgements can be made distinguishing between true biochemical abnormalities from a presumably rather large range of normal values.

Concentrations of Other Electrolytes

There is little to no evidence that other electrolytes have any role in establishing an increased risk for caries. Duggal et al. (1991) reported an inverse relationship between salivary copper concentrations and caries status but found no consistent relationship regarding the levels of iron, manganese and zinc. The salivary concentration of magnesium was found to be inversely related to caries progression in the two Woltgens et al. (1992) studies, but this again held true only for girls and not for boys. Two papers suggest that caries risk is associated with increased salivary levels of sodium [45, 46] while one suggests just the opposite (Ryberg et al., 1991), and three report no relationship between salivary sodium and caries (Dodds et al., 1997; Lenander-Lumikari et al., 1998; and Pedersen et al., 1999). Two studies suggest an inverse relationship between salivary potassium and

caries [12, 45], one study suggests that potassium levels are slightly increased in caries-active subjects [24], and two report no relationship between salivary potassium and caries [10, 69]. One study found that chloride levels are slightly increased in caries-active subjects [24] whereas another found no relationship between chloride and caries [45]. From the limited evidence available, no clear pattern emerges when one evaluates the potential role of these other electrolytes in determining caries risk.

Concentrations of Other Small Molecules

There is also little to no evidence that other salivary small molecules have any role in establishing an increased risk for caries. Two studies found that salivary concentrations of the basic free amino acids arginine, lysine and/or histidine are inversely correlated with caries experience [70, 71], suggesting that they may have a role in neutralizing plaque acids. Interpretation of this information is complicated, however, by the wide range of reported values for the measurement of amino acid concentrations in saliva. One study reported an inverse relationship between the concentration of urea in saliva and caries [46] while two others found no such relationship with urea or uric acid [24, 45]. One paper provided equivocal evidence for the relationship between the acetic acid-acetate buffer system and caries [72], but no data on actual pH measures were reported. Only one paper reported an inverse relationship between hypothiocyanite levels in saliva and caries [16] while three others found no such relationship with hypothiocyanite or thiocyanate [30, 50, 69]. One paper reported a possible relationship between caries and hexosamine levels in saliva [12]. From the limited evidence available, no clear pattern emerges when one evaluates the potential role of these small molecules in determining caries risk.

Other Relevant Evidence

Two studies published prior to 1986 reported no relationship between caries status the levels of thiocyanate and hypothiocyanite in saliva (Mandel *et al.*, 1983; Lamberts *et al.*, 1984); these are further discussed below under “Other Relevant Evidence” in Question Number 3.

Question Number 3: Are individuals with teeth and altered salivary composition with respect to macromolecules at increased risk for dental carious lesions compared with individuals of the same age and dentition with normal salivary macromolecular composition?

Salivary Immunoglobulins

The literature demonstrates that there has been considerable interest in establishing whether or not salivary immunoglobulins may be protective against caries. Of the 22 studies which reported results examining the relationship between salivary immunoglobulins and caries status, all of them evaluated secretory IgA and a few also examined IgG and IgM as well as bacterial agglutination rates [73, 74, 81, 75, 76, 82, 83, 87, 84, 29, 30, 16, 77, 80, 78, 85, 79, 12, 86, 45, 46, 50]. In one instance, data were published in both abstract and full-length manuscript forms (Rose *et al.*, 1993 and 1994). Eleven studies examined unstimulated whole saliva and seven examined stimulated whole saliva. Five studies examined unstimulated parotid saliva and two examined stimulated parotid saliva. No studies separately examined secretions from submandibular/sublingual or minor salivary glands. The method of stimulation was masticatory for whole saliva and gustatory for parotid secretions. None of the studies specifically evaluated root caries and these studies were equally distributed in evaluating primary and permanent teeth.

The studies make a distinction between the levels of total IgA in saliva and the levels of specific IgA antibodies against cariogenic bacteria, most notably species of mutans streptococci. The rationale, simply stated, is that it is not so important how much antibody one has in general, but rather how much of a particular antibody possessing activity against caries-associated microbes. The vast majority of the evidence indicates that the measure of total IgA in saliva is not useful in identifying

caries risk. Eleven papers reported no clear relationship between total IgA and caries [16, 29, 30, 50, 73-79] while three reported an inverse relationship between concentrations of total IgA in saliva and caries experience [45, 46, 80]. Although the reasons for this disagreement between the former and latter studies are unknown, the available evidence does not support a role for total salivary IgA in caries risk assessment.

The literature is nearly equally divided for or against an anti-caries role of specific salivary IgA. Seven studies reported an inverse relationship between specific IgA antibodies (ex. anti-S. mutans IgA) and caries status [74, 79, 81-85], two studies reported that caries was related to increased levels of specific IgA [80, 86], and five studies reported no relationship between specific IgA immunoglobulins and caries [16, 29, 30, 77, 87]. With one exception (Kirstila et al., 1994) these reports examined subjects who were healthy or had medical conditions not directly related to immunoglobulin deficiency. Kirstila et al. (1994) compared individuals with common variable immunodeficiency (CVI) to healthy control subjects. The CVI patients all were on immunoglobulin-replacement therapy (median duration 10 years; range 2-25 years) which had normalized the levels of IgG but not IgA or IgM in saliva or serum. For both primary and permanent teeth, these investigators found no significant difference in the number of decayed, missing, and filled teeth or tooth surfaces between CVI and control subjects. Because they also found no difference in salivary flow rate, buffer capacity, lysozyme, lactoferrin, and peroxidase activity between the two groups the authors concluded that "backup" systems likely exist in saliva. Such functional redundancy probably accounts for the mixed evidence available for the other studies as well. Nonetheless, if one sorts the studies non-rigorously into two groups, about twice as many studies show some possible relationship between specific IgA levels and caries in comparison with those studies showing no relationship at all.

Of the studies which also determined levels of salivary IgG or IgM only one reports any association with caries experience. Kirstila et al. (1998) found an inverse relationship between total IgG and caries incidence over two years but a directly proportional relationship between anti-S. mutans IgG and caries over this same time period. However, these data are difficult to interpret due to the low caries incidence found in the study group. Less than 25% of the subjects developed new caries over the two year period; of those who did, DMFT and DMFS was rather low (both less than 1.0). Insufficient data exist to allow statements on salivary IgM levels or on agglutination rates of IgA, IgG, and IgM.

Taken all together, there is moderate evidence that caries risk can be determined by quantifying the levels of specific IgA immunoglobulins directed against cariogenic microorganisms. However, there is insufficient consistency to allow use of this measure as a diagnostic tool in clinical practice. There is insufficient evidence to establish whether or not the salivary gland stimulation status is important in this regard, or if such risk is different for crown vs. root surfaces, different aspects of crown surfaces, or for primary vs. permanent teeth. There is reasonably clear evidence that measurement of total IgA in saliva is not a useful marker for caries risk. There is insufficient evidence to draw conclusions about IgG or IgM. Evidence from immunocompetent subjects as well as individuals with humoral immunodeficiency suggests that non-immunoglobulin defense mechanisms function in parallel with the immunoglobulin-mediated system and have the potential to compensate for deficiencies in antibody function.

Salivary Innate Non-immunoglobulin Factors

As just mentioned above, saliva contains a number of innate defense factors that may modify caries risk. Fourteen studies examined the relationship between caries and one or more of the following salivary factors: total protein; acidic or basic proline-rich proteins (PRP); histatins; statherins; sucrase activity; amylase; peroxidase/myeloperoxidase; lysozyme, lactoferrin; salivary glycoconjugates; and bacteria-aggregating glycoproteins (BAGP) [10, 12, 24, 29, 30, 40, 45, 46, 50, 58, 69, 83, 88, 89]. Slightly more studies examined stimulated whole saliva rather than unstimulated whole saliva (8 vs. 5, respectively). More studies examined stimulated parotid saliva rather than unstimulated parotid

saliva (6 vs. 1, respectively). No studies separately examined secretions from submandibular/sublingual or minor salivary glands. The method of stimulation was masticatory for whole saliva and gustatory for parotid secretions. None of the studies specifically evaluated root caries and about one-third of these studies evaluated primary teeth in addition to permanent teeth.

Nearly all the studies found no relationship between caries and any of these various salivary factors. For example, at least five studies failed to demonstrate any significant relationship between lysozyme and caries [12, 30, 50, 77, 83] whereas only one study reported an inverse relationship between lysozyme concentration and caries activity [45]. This latter study is the only one which also found any association between caries and salivary amylase; in this instance caries was associated with an increased level of amylase. Five studies found no significant relationship between caries and lactoferrin levels in saliva [29, 30, 50, 69, 83]. Kirstila et al. (1994) found a slightly increased level of total salivary peroxidase in subjects with common variable immunodeficiency, but this does not appear to be clinically relevant. Only the study by Ryberg et al. (1991) found a relationship between caries and diminished total protein output. Only two studies evaluated PRPs or statherins [10, 24] and only one study examined histatins [24]; none of these studies found any relationship to caries. Collectively, these studies provide little to no evidence for any direct relationship between these various components in saliva and the risk for caries.

Other Relevant Evidence

As indicated above, questions exist regarding the protective role that salivary humoral immunity may have against dental caries in humans. This can be further illustrated by several additional reports which were not included in the present review, but that provide contrasting information on the role of total IgA. In two reports published before 1986, Legler et al. (Legler *et al.*, 1981; Legler *et al.*, 1982) found that immunodeficient individuals appear to have an increased susceptibility to caries when compared with immunocompetent subjects. These two publications provide slightly different presentations of the same data from one study of 45 immunodeficient individuals, 22 of whom had selective IgA deficiency. When compared to healthy controls, the immunodeficient patients had significantly higher DMFT and DMFS scores. On the other hand, Fernandes et al. (Fernandes *et al.*, 1995) studied subjects with total (n=9) and partial (n=3) IgA deficiency and reported that the IgA-deficient subjects actually had caries scores lower than those of healthy controls, but presented with much higher levels of IgM. This latter finding is in general agreement with those of Kirstila et al. (1994 and 1998) discussed above, that collectively suggest that immunodeficient individuals demonstrate one or more compensatory salivary mechanisms (both immune and non-immune) which may obviate any increased caries risk. It should again be pointed out that measures of total IgA, rather than specific IgA, may not be useful in establishing caries risk; such an observation was noted by Mandel's group in the 1970's (Stuchell and Mandel, 1978). Taken all together, the literature evaluating caries risk in subjects with humoral immunodeficiency do not report a consistent pattern.

The older literature also reports contradictory information about the non-specific immune factors such as lysozyme and lactoperoxidase. MacKay et al. (MacKay *et al.*, 1984) found that there was considerable interindividual variation in salivary lysozyme levels and that no significant differences in lysozyme concentration were noted between caries-resistant and caries-susceptible adults. In contrast, Twetman et al. (Twetman *et al.*, 1981) reported that lysozyme may impart resistance to caries in children. However, such an age-dependent relationship has not been definitively established. Mandel et al. (Mandel, *et al.*, 1983) had earlier reported that the salivary concentrations of lactoperoxidase, thiocyanate, and hypothiocyanite were not critical determinants of caries resistance or susceptibility. A similar conclusion was reached by Lamberts et al. (Lamberts, *et al.*, 1984), who further observed that single point measurements of static properties of saliva may be insufficient to reveal significant correlations with caries activity.

Regarding other salivary proteins, we point out that Mandel and Bennick (1983) (Mandel and Bennick, 1983) found no relationship between caries status and the salivary levels of acidic PRPs. This contrasts with work published in 2000 that indicates differences in basic PRPs between

individuals who have remained caries-free and those who have experienced dental decay (Ayad *et al.*, 2000). One group (Shomers *et al.*, 1982) reported no difference in the levels of cysteine-containing phosphoproteins between caries-resistant and caries-susceptible subjects. A quite recent paper examining 209 healthy subjects reported a negative correlation between carbonic anhydrase and DMFT (Kivela *et al.*, 1999). This paper was excluded from review, however, because it was a descriptive study falling into AHRQ level III.

We note here that several studies by Slomiany and co-workers indicate a role for salivary lipids, phospholipids and mucous glycoproteins (i.e., mucins) in determining caries risk (Slomiany *et al.*, 1982; Murty *et al.*, 1985; Slomiany *et al.*, 1986a; Slomiany *et al.*, 1986b; Murty *et al.*, 1987; Slomiany *et al.*, 1987a; Slomiany *et al.*, 1987b; Slomiany *et al.*, 1990; Piotrowski *et al.*, 1992a; Piotrowski *et al.*, 1992b; Slomiany *et al.*, 1993). These articles were not included in the evidence tables because they were published earlier than 1986 and/or they utilized fewer than 30 subjects total. Nonetheless, these reports collectively suggest that differences in these molecular species may account for differences observed between caries-resistant and caries-susceptible individuals. The potential protective functions of salivary mucins have been reviewed by Nieuw Amerongen *et al.* (Nieuw Amerongen *et al.*, 1995).

Question Number 4: Are individuals with teeth and diagnosed medical conditions/diseases which affect saliva at increased risk for dental carious lesions compared with individuals of the same age and dentition who do not have medical conditions/diseases which affect saliva?

The available evidence for a relationship between caries susceptibility and medical conditions known to affect salivary physiology can be grouped into three main categories, according to the etiology of the salivary gland dysfunction. One category includes those autoimmune conditions which alter salivary function such as Sjögren's syndrome. Another category includes studies of subjects who have iatrogenic complications of their salivary glands following medical treatment, such as occurs after radiation therapy for tumors of the head and neck region. The third main grouping involves salivary alterations that occur as a side effect of any number of prescription medications, such as certain antihypertensive agents which lead to dry mouth. A fourth grouping lumps together the evidence related to several other conditions (including humoral immunodeficiency) for which literature is available.

Sjögren's Syndrome and Associated Conditions

Sjögren's disease is an autoimmune exocrinopathy that results in clinically significant oral dryness. It manifests itself as a syndrome, primarily affecting women, that is classified as either primary or secondary. Primary Sjögren's syndrome (pSS) involves both ocular dryness (keratoconjunctivitis sicca) and oral dryness (xerostomia) in the absence of any other major disease (usually of connective tissue). Secondary Sjögren's syndrome (sSS) involves either ocular or oral dryness associated with other connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. Approximately 50% of sSS is associated with rheumatoid arthritis. The remainder tends to be associated with systemic lupus erythematosus or scleroderma, usually in this descending order of occurrence. It is somewhat surprising, therefore, that our search methodology found very little information regarding sSS, especially that associated with rheumatoid arthritis.

Five studies examined the relationship between caries risk and Sjögren's syndrome. Of these, three evaluated both pSS and sSS groups of subjects [1, 8, 90] and the remaining two evaluated subjects having only pSS [10, 11]. These studies were roughly equally divided in examining unstimulated whole saliva and/or stimulated whole saliva (4 vs. 3, respectively). Two of the studies examined stimulated parotid saliva and none evaluated unstimulated parotid saliva. No studies separately examined secretions from submandibular/sublingual or minor salivary glands. The method of

stimulation was masticatory for whole saliva and gustatory for parotid secretions. Only one of the studies specifically evaluated root caries in addition to crown caries [11] and one examined “cervical” decay [90]. All of the studies evaluated permanent teeth and none of them evaluated primary teeth.

The salivary parameters measured involved mainly flow rate (4 studies), buffer capacity (1 study), and pH (2 studies). One study utilized self-reported oral dryness based on subjects’ use of a visual analog scale [90]. Only one of the studies measured salivary electrolytes or macromolecular components; this was the study of Pedersen et al. (1999), also discussed under Questions Number 2 and 3 above, that measured levels of sodium, potassium, statherins and acidic PRPs and found no relationship with caries status. All of these studies found that individuals with both pSS and sSS had significantly diminished flow rates of unstimulated whole saliva, stimulated whole saliva, and stimulated parotid secretion. All the studies reported that this diminished salivary flow rate had a strong relationship with caries experience, in general. However, the distinction between caries susceptibility in pSS vs. sSS subjects is not clear. For example, the paper by Almstahl et al. (1999) found that only the pSS subjects, but not the sSS subjects, had significantly more filled carious surfaces when compared to their respective control groups. On the other hand, Najera et al. (1997) and Soto-Rojas et al. (1998) reported no difference between pSS and sSS groups, and both pSS and sSS subjects had significantly higher caries scores than the respective control groups. The latter study further noted that cervical or atypical caries was noted in 83% of the Sjögren’s subjects. Neither pSS nor sSS subjects had any discernible alterations in mean salivary pH or buffer capacity, and these were not associated with caries risk in these studies.

On the basis of these studies it appears that the chronic and clinically significant reduction in salivary secretion that occurs in Sjögren’s syndrome is a definite risk factor for caries development. Thus, a normal quantity of saliva seems to have a caries-protective effect. No such statement can be made about the quality of saliva due to the lack of evidence. It should also be noted that there is little to no evidence to suggest that normal healthy individuals have idiopathic alterations in salivary secretion rates that predispose them to caries. Due to the little available evidence, no definitive statements can be made whether or not the salivary gland stimulation status is important in caries risk. Since the studies focused only on whole saliva or parotid secretion, there is no evidence for any role specifically of submandibular/sublingual or minor salivary gland dysfunction in increasing caries risk in Sjögren’s patients. There is no evidence to suggest that the method of salivary stimulation (i.e., masticatory or gustatory) is related to caries risk. Sjögren’s syndrome is considered to be a disease of adults. Consequently, none of the studies examined primary teeth and no distinct statement can be made about the caries risk in primary vs. permanent teeth. There is, however, some limited evidence to indicate that the risk for caries due to low salivary secretion in Sjögren’s patients is different for crown vs. root surfaces and for different aspects of crown surfaces. Most notably, these individuals appear to have an enhanced susceptibility towards cervical decay.

Scleroderma is a connective tissue disorder manifesting systemic sclerosis that can be associated with Sjögren’s syndrome. As with Sjögren’s, this condition principally affects women. One study found a relationship between scleroderma-related xerostomia and caries prevalence [91]. In this study xerostomia was determined objectively by visual grading of oral dryness by the examiners. Xerostomia was present in 70% of scleroderma patients (vs. 10% of healthy control subjects) and was significantly associated with an increased frequency of dental caries. Scleroderma subjects who did not have xerostomia also did not have any higher risk of caries when compared to control subjects. None of the patients were taking any medications with xerostomic side effects. This report provides further evidence that medical conditions which affect salivary flow can increase the risk of caries in the affected individuals.

One additional study examined juvenile chronic arthritis, but found no difference in salivary flow rates between the test and control groups [45]. Thus, no statement can be made about the role of arthritic conditions and caries susceptibility.

Radiation Therapy, Chemotherapy, and Surgical Therapy

Damage to salivary glands can be a transient or permanent sequela of certain medical treatments, especially those for cancer of the head and neck area. Such damage can be direct or indirect and can, in theory, result from radiation therapy, chemotherapy or surgical treatment of the salivary glands or ducts. There is no doubt that salivary glands are particularly susceptible to radiation damage of the head and neck area. Although the extent of damage to the salivary glands depends in part on the dosage of the radiotherapy as well as on the efficacy of any shielding, it is clear that permanent partial or total dysfunction is a usual result in cancer patients treated by head and neck local radiation. It is very surprising, therefore, that our search methodology found no controlled studies examining the caries risk in this group of subjects. We note here that the literature contains a number of excluded case reports dealing with this topic. The excluded descriptive and comparative studies often assumed an increased risk of caries as a consequence of salivary hypofunction, without actually measuring the caries prevalence or incidence.

Seven studies examined subjects who had received radiation or chemotherapy mainly to treat malignancies such as the different forms of leukemia, in addition to other conditions. Of these, five examined subjects who had received only chemotherapy without any radiation to the jaws [34, 43, 58, 60, 75] and two evaluated groups of subjects who had received a combination of total body irradiation and chemotherapy (i.e., bone marrow transplant patients) in comparison with subjects receiving only chemotherapy or with healthy controls [23, 37]. The majority of the studies examined masticatory stimulated whole saliva when compared to those studying unstimulated whole saliva (6 vs. 1, respectively). None of these studies separately examined secretions from parotid, submandibular/sublingual or minor salivary glands. Five of the studies examined both primary and permanent teeth and none of the studies specifically evaluated root caries in addition to crown caries.

The salivary parameters measured involved mainly flow rate (5 studies), buffer capacity (4 studies), and pH (2 studies). Only two of the studies also measured salivary electrolytes or macromolecular components; these were the studies of Dens et al. (1995) which measured total IgA and IgG and Pajari (1998) which measured total IgA, IgG and IgM as well as lysozyme. The evidence regarding immunoglobulins and lysozyme from these latter two papers has been also discussed under Question Number 3 above. Collectively, all these studies failed to find a relationship between chemotherapy and increased caries risk. Interestingly, total body irradiation also was not a factor in determining caries risk, despite the permanent salivary dysfunction observed [Dahloff et al. (1997) and Nasman et al. (1994)]. It should be noted, however, that with the exception of one child in the Pajari (1988) study the evidence table does not include any studies specifically evaluating the relationship between caries and local radiation to the jaws. As we indicated above, this is an important distinction because there is a body of evidence from older literature (before 1986) which supports the belief that local irradiation to the glands leads to diminished salivary flow that in turn leads to increased caries susceptibility, similar to Sjögren's syndrome.

It should also be noted that most of the studies found no difference in caries status between the test and control groups [23, 34, 37, 43, 58]. As discussed above under Question Number 1, this makes interpretation of the evidence regarding salivary flow rate or buffer capacity somewhat equivocal. For example, Dahloff et al. (1997) reported that despite a significantly decreased flow rate in subjects receiving total body irradiation, no significant correlation was found between caries incidence over four years and salivary flow rate. This observation may have been confounded, however, by the physiologic increase in salivary flow rate which tends to occur with age in children. Variable oral hygiene regimens among study groups may have been another confounding variable. For example, in the study of Nasman et al. (1994), the group receiving total body irradiation appeared to have had a more intensive fluoride and chlorhexidine regimen than the comparison groups. The length of time in remission did not appear to be a factor that had any influence on caries or salivary status (Sepet et al., 1998).

Collectively, the studies indicate that total body irradiation prior to bone marrow transplantation may or may not lead to permanent salivary dysfunction, that chemotherapy may lead to transient but not

to permanent alterations to salivary function, and that overall neither significantly increases the risk of caries. Due to the little available evidence, no definitive statements can be made whether or not the salivary gland stimulation status is important in caries risk. Since the studies focused only on whole saliva there is no evidence for any role specifically of parotid, submandibular/sublingual or minor salivary gland dysfunction in increasing caries risk in cancer patients. There is no evidence to suggest that the method of salivary stimulation (i.e., masticatory or gustatory) is related to caries risk. Since the majority of the studies examined both primary and permanent teeth, it seems that there is no difference in the caries risk of primary vs. permanent teeth. Since none of the studies specifically evaluated root surfaces, no statement can be made whether or not the risk for caries in cancer patients is different for crown vs. root surfaces and for different aspects of crown surfaces. The limited evidence available also suggests that it is the medical treatment of these conditions rather than the disease per se that may have any relationship to caries risk.

In addition, one study examined subjects who had received surgical repositioning of sublingual salivary ducts (sialodochoplasty) to decrease drooling in cerebral palsy patients [62]. This study evaluated coronal caries in primary and permanent teeth in relationship to the buffer capacity of unstimulated whole saliva. Although cerebral palsy subjects treated surgically had more caries than those treated nonsurgically, no difference in buffer capacity was found. The reason for the increased caries prevalence in the surgical group is not clear because qualitative assessment of salivary flow indicated no decrease in salivary output. Moreover, the salivary flow in these patients is generally quite high. No studies of subjects having received surgery to the salivary glands per se were included in this review.

Use of Medications having Xerostomic Side Effects

Diminished salivary flow rate is associated with many medications having anti-cholinergic or anti-adrenergic properties that are known to exhibit xerostomic side effects; for example, anti-hypertensive agents, anti-secretagogues, and psychotropic agents. Interestingly, there are relatively few controlled studies after 1986 which have specifically examined the caries status of individuals using xerostomia-inducing drugs. Most of the evidence appears to be in the form of case reports, which were excluded from the present review, or from studies evaluating oral dryness due to medications that assumed, but did not actually measure, an associated increased risk for caries; these latter types of studies were also excluded from the present review.

We found seven studies that evaluated caries risk due to medication use for a wide variety of minor and major medical conditions (excluding cancer chemotherapy as discussed above) [4, 12, 13, 32, 35, 92, 93]. About half of these studies provide evidence that certain medications can lead to increased caries risk. Using the subjective measure of self-reported dry mouth, one study [92] longitudinally followed more than 600 generally healthy subjects over 18 months and found that in bivariate correlations the incidence of coronal caries in black subjects, but not white subjects, was inversely associated with the use of antihistamines. When data were analyzed by multivariate logistic regression, however, these investigators found that the incidence of coronal caries in white subjects, but not black subjects, was significantly associated with the use of antihistamines. Such findings are difficult to interpret and the authors acknowledge that there may have been other unknown factors influencing their results, including the appropriateness of using self-reported dry mouth rather than objective measures of salivary status. Also for the most part, the available literature does not provide clearly discernible racial differences in salivary response to medications. The potential increased caries risk due to asthma medications was evaluated in the two papers by Ryberg et al. (1987 and 1991) which represent baseline and four-year follow-up studies, respectively. These investigators measured a number of salivary parameters and reported that caries incidence was higher in the asthmatic group when compared to healthy controls. The asthmatic subjects also had a 20-35% decrease in salivary flow rates when compared to the control group. However, when low-caries and high-caries subsets of the asthma group were compared, mean whole saliva flow rate in both subsets were found to be within normal ranges and not significantly different from each other. Again, this makes interpretation of the evidence somewhat confusing. Stiefel et al [13] examined

psychotropic medication use by individuals suffering from chronic mental illness and reported higher coronal smooth surface caries and lower flow of unstimulated whole saliva. However, potential technical problems with the saliva collection and analysis method may have confounded the results. It is interesting to note, nonetheless, that these authors found no caries risk associated with the specific use of lithium in their subjects; lithium induces hyposalivation in the majority of subjects who use it. The remaining studies found no clear association between caries and medication use.

Although somewhat limited, the evidence reported here continues to support the belief that certain medications that have xerostomic side effects may lead to an increased risk of caries. Such a risk appears to be the result of lowered salivary flow rate rather than other alterations in saliva, for example, buffer capacity. The risk does appear to involve crown surfaces but no definite statement can be made for root surfaces, or for primary vs. permanent teeth. It should also be noted that none of the studies measured the effect of discontinuing medication on salivary output. Therefore, these findings could be inaccurate regarding the "increased risk" for dental caries.

Other Conditions

In addition to the medical problems already discussed, a number of articles which attempted to correlate caries with salivary disturbances in other conditions were found. These include both insulin- and noninsulin-dependent diabetes [35, 39, 51, 52, 54, 94], anorexia and bulimia [9, 17, 53, 63], chronic malnutrition [7], Crohn's disease [50], cleft lip and cleft palate [2], various heart conditions [32, 35, 76], chronic renal failure [27], common variable immunodeficiency, previously described above [30], asthma, also as previously described above [12, 31, 69, 93], Down's syndrome and non-Down's mental retardation [95, 96], spinal cord injury [14], and thalassemia major [46]. None of these articles provided convincing evidence linking caries with salivary dysfunction in any of these conditions. It should be noted that a few case reports were found that described increased caries in subjects having agenesis or hypogenesis of the salivary glands, but these were not included in this report. It should also be noted that several of the articles included in this review indicate that salivary function might be affected by certain subject-related conditions such as age, gender, race, diet, smoking and stress, but these were not specifically evaluated as part of this report.

Other Relevant Evidence

Consistent with the increased caries found in diseases known to produce Sjögren's-like symptoms, one article (Richards *et al.*, 1994) reported the case of a 55-year-old woman with primary biliary cirrhosis who exhibited what the authors described as rampant dental caries of rapid onset. Two articles focusing on children with cystic fibrosis found an inverse relationship between caries status and the salivary pH and buffering capacity (Kinirons, 1983; Kinirons, 1985). Specifically, it was noted that children suffering with cystic fibrosis exhibited a low caries experience presumably due to the high buffering activity also found in these patients. Two additional excluded articles found no differences in salivary flow rate, buffering capacity or protein levels in subjects with Crohn's disease when compared to controls, regardless of the caries status of the comparison groups (Halme *et al.*, 1993; Sundh *et al.*, 1993). One of the excluded studies reported some evidence linking the low caries activity in patients with chronic renal failure to alterations in urea metabolism (Peterson *et al.*, 1985). An additional paper studied chronic lithium use in 14 manic-depressive patients (Markitziu *et al.*, 1988). Similar to results discussed above, this particular report found no significant correlation between lithium use and DMF index in the subjects. Two descriptive studies examined subjective reports of mouth dryness in relation to medication use. Locker (1993) found that subjects with oral dryness had more decayed crown but not root surfaces. In contrast, Gilbert *et al.* (1993) found that caries was more prevalent in persons who reported dry mouth, but that there was no statistically significant difference between the dry mouth and non-dry mouth groups. Additional information about medication-related mouth dryness can be found in a study by Loesche and co-workers (Loesche *et al.*, 1995).

IV. CONCLUSIONS

Summary of Main Findings/Gaps in Evidence

The overall key question of clinical importance addressed in this evidence report is, "Is there evidence that saliva is a risk factor for dental caries in humans?" To answer this question we focused on both quantitative and qualitative aspects of saliva to evaluate the relationship between caries and salivary status. Salivary parameters deemed important were salivary flow rate, buffer capacity, pH, glucose clearance rate, the salivary constituents belonging to the immune and non-immune defense system, and the salivary constituents involved in non-defense functions such as tooth mineral regulation. The aim of our analysis was to establish the clinical relevance of salivary status in determining caries risk. As indicated above, it should be emphasized that the evidence for a protective effect of fluoride treatment was not reviewed in the present work because it falls outside the "risk" scope of this report.

Considerable individual subject variations in the physico-chemical aspects of saliva were reported in many of the studies reviewed. This was observed for longitudinal measurements as well as single time-point evaluations. Nonetheless, the preponderance of the literature supports the belief that a normal salivary flow rate imparts a strong protective effect against caries (see Summary Table 2). Significantly diminished salivary flow rate is associated with a number of predisposing medical conditions; most notably Sjögren's syndrome, radiation-induced damage to the salivary glands, and the use of a variety of medications which result in xerostomia as a side effect. Although not as strong as for flow rate, there is also reasonably good evidence to support a protective role due to salivary buffering capacity. Individuals with significantly diminished ability to neutralize acids seem to be at higher risk for caries; however, such a condition appears to be related to idiopathic differences among individuals rather than to any clearly discernible medical problem. Regarding salivary immunoglobulins, the literature is nearly equally divided for or against a protective role against caries due to these macromolecules, especially secretory IgA. Interestingly, studies evaluating caries risk in subjects with humoral immunodeficiency do not report a consistent pattern. Regarding non-immunoglobulin defense macromolecules such as salivary peroxidase, lysozyme, lactoferrin, histatins, and other salivary antimicrobial proteins, sparse evidence suggests a protective role against caries. Finally, there is insufficient evidence to determine whether or not naturally occurring salivary electrolytes and small molecules provide a significant protective effect against caries.

Generalizability of the Findings

The findings of the present review are in overall good agreement with those of the earlier review by Rudney (Rudney, 1995), who also described the problems involved in relating saliva to oral health. In brief, not only are experimental characteristics such as study design, appropriateness of assay conditions and minimization of confounding variables (ex. circadian variation) important in clinical studies, but also are the fundamental biologic processes which can result in wide intra- and intersubject variability in any number of potential caries risk factors. The latter processes are not sufficiently understood to allow accurate and precise assessments of caries risk for all individuals; however, reasonably good assessments can be made for groups of individuals, especially those in clearly high-risk groups (ex. Sjögren's syndrome). We also indicated above that multivariate analyses have not borne out the significance of salivary factors in establishing caries risk, when other factors are concomitantly evaluated. This can be further illustrated by one of the excluded articles that presented data from a very large descriptive study (n=2,800 subjects) which examined bivariate and multivariate correlations between caries prevalence and a number of factors, including flow rate and buffer capacity (Granath *et al.*, 1991). These latter two parameters ranked low in order of importance in contrast to factors such as prior history of caries, lactobacillus counts, mutans streptococci counts, and oral hygiene index. The authors could not explain the results with salivary flow rate and buffer capacity and concluded that these measures may be unsatisfactory to explain caries risk in observational studies.

These difficulties notwithstanding, considerable effort has been and is continuing to be made to develop and perfect models for caries risk assessment that will have sufficiently high sensitivity and specificity to be used to indicate and predict risk on an individual basis. A good example of this are the two companion papers of Leverett *et al.* (Leverett *et al.*, 1993a; Leverett *et al.*, 1993b) that evaluated cross-sectional and longitudinal discrimination models for the assessment of caries risk. In these studies, for example, stimulated whole saliva was collected for analysis of fluoride concentration. This latter parameter was one of seven study variables found by discriminant analysis to allow a distinction between individuals with zero caries vs. high caries (DMFS \geq 6). The sensitivity and specificity was found to be better than 70%. However, such information from research studies has not yet made the transition into day to day clinical practice. We also note several previously published reviews that may complement the present report (Anonymous, 1988; Anonymous, 1992; Wefel, 1995; Bratthall *et al.*, 1996).

“Take-home Message”

Saliva provides a general protective function for exposed oral hard tissues such as enamel and dentin. A clinically significant decrease in salivary flow can be considered an important factor contributing to caries risk. Consequently, clinicians should identify individuals with reduced salivary output and modify their treatment and prevention programs in ways that diminish the risk of caries. To a lesser degree of certainty, it can be also concluded that individuals whose salivary buffering capacity is reduced have a higher risk for caries. Thus, the general salivary parameters of flow rate and buffer capacity can be considered to be clinically useful diagnostic indicators. No convincing evidence is presently available that other more specific characteristics of saliva are useful in indicating or predicting an increased risk of caries and this includes evidence on the salivary immune and non-immune systems. It is possible that this lack of correlation is due to the multiple levels of salivary redundancies discussed in the Introduction.

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VII. SUMMARY TABLES

SUMMARY TABLE 1. Distribution of the principal studies describing physical and chemical aspects of saliva as indicators of risk for dental caries in humans.

Salivary Characteristic or Medical Condition	Reference Numbers (n studies)		
	Anticaries Association	No Association with Caries	Procaries Association
Flow Rate	1-21 (21)	22-55 (34)	94 (1)
Buffering Capacity	4-7, 9, 15, 19, 25, 38, 56, 57 (11)	1, 17, 22, 24, 26, 28, 30, 32, 34-37, 39-42, 47-49, 51, 52, 54, 59- 65 (29)	(0)
Glucose Clearance Rate/Concentration	(0)	18, 32, 42, 51, 52, 54, 66 (7)	(0)
Calcium/Phosphate	12, 20, 21, 45, 46, 67, 68 (7)	24, 69 (2)	(0)
Other Electrolytes & Small Molecules	(0)	10, 12, 16, 24, 30, 45, 46, 50, 69, 70-72 (12)	(0)
Specific sIgA Immunoglobulin	74, 79, 81-85 (7)	16, 29, 30, 77, 87 (5)	80, 86 (2)
Innate Non- immunoglobulin Factors	(0)	10, 12, 24, 29, 30, 40, 45, 46, 50, 58, 69, 83, 88, 89 (14)	(0)
Sjögren's Syndrome & Associated Conditions	(0)	(0)	1, 8, 10, 11, 90, 91 (6)
Chemotherapy & Total Body Irradiation	(0)	23, 34, 37, 43, 58, 60, 75 (7)	(0)
Local Radiation (Head & Neck Area)	see text for description		
Medications with Xerostomia Side Effect	(0)	4, 32, 35 (3)	12, 13, 92, 93 (4)
Other Medical Conditions	(0)	2, 7, 9, 12, 14, 17, 27, 30-32, 35, 39, 46, 50-54, 63, 69, 76, 93- 96 (25)	(0)

SUMMARY TABLE 2. Evidence ranked according to the strength of association between salivary characteristics and caries risk.

Strong Association with Caries Risk	Weak-to-Moderate Association with Caries Risk	No Association with Caries Risk
Flow Rate	Buffering Capacity; Calcium/Phosphate; Specific sIgA Immunoglobulin	pH (static measurement); Glucose Clearance Rate/Concentration; Other Electrolytes & Small Organic Molecules; Total sIgA; IgG, IgM, Innate Immunity Factors

VIII. FIGURE 1.

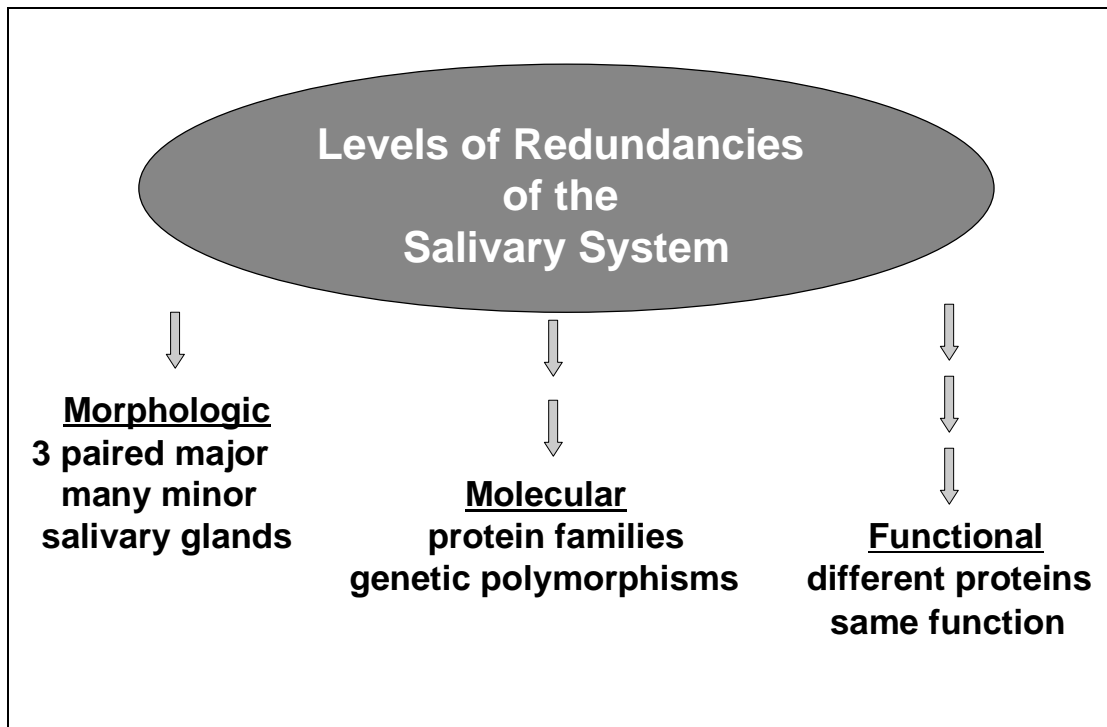


FIGURE 1. Schematic summary of the biological considerations in interpreting the clinical evidence of the relationship between saliva and caries risk. There are several levels of redundancies in the salivary system that likely have evolved over time to ensure maximal protective effects to the organism. For example, there are three paired major salivary glands all of which secrete important protective factors. Mineral homeostasis is maintained by a number of proteins, such as the proline rich proteins, statherin, cystatin and histatin 1. Antimicrobial activity is provided by sIgA and several factors of the innate immune system, including peroxidase, lysozyme, lactoferrin and the histatins. Clearly, this redundancy complicates identification of any one specific salivary quality to be strongly associated with anticaries function. Rather, it appears that these myriad protective mechanisms work in combination and provide needed “backup” when necessary.

IX. ATTACHMENTS

Attachment A. Table/Reasons of Excluded Studies

Attachment B. Data Extraction Form

Attachment C. Evidence Tables 1A, 1B & 1C

**Evidence Table 1A: General Description and Experimental
Design Characteristics of the Included Studies**

**Evidence Table 1B: Caries Status Assessments and Saliva
Status Assessments used in the Included Studies**

**Evidence Table 1C: Clinical Evidence for the Presence of a
Protective Effect of Saliva against Caries**